language in accordance with the Examiner's suggestion. None of the amendments made herein constitutes the addition of new matter.

The Rejections under 35 U.S.C. 101

Claims 16-20 have been rejected under 35 U.S.C. 101, as allegedly lacking utility. Applicants respectfully traverse this rejection.

The claims are directed to a method for cleaving double-stranded DNA containing a broad scope of DNA lesions wherein the proteins used for cleavage are identified by SEQ ID Nos:36-39. The sequences were identified as homologs of the *S. pombe* UVDE. The Examiner has noted that the homology is unknown because Table 19 was not included in the Specification. This is correct; however, the homology in inherent within the sequences and Applicants provide Exhibit A herewith an alignment of the referenced sequences with that of UVDE.

Although Applicants have not provided data related to the noted enzymes, Applicants have stated that the noted enzymes carry out their claimed function. The Examiner has not provided any sound scientific reasoning, scientific evidence or affidavit to support the refusal to accept Applicants' statements. Applicants have provided statements as to the biological significance of the noted proteins, and utility has been taught. In the absence of a reasoned refusal to accept Applicants' statements, the rejection should be withdrawn.

The Rejections under 35 U.S.C. 112, first paragraph

Claims 16-20 have been rejected under 35 U.S.C. 112, first paragraph, as the claimed invention is allegedly not supported by a specific and substantial utility or a well established utility as discussed above. Applicants respectfully traverse this rejection.

The Patent Office has alleged that one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

Applicants respectfully disagree with the Patent Office position. Applicants have taught previously unknown activities of the noted enzymes. The Examiner has presented no evidence, sound scientific reasoning or affidavit to support the refusal to accept Applicants' statements as to the utility of the invention, as required (see, e.g., In re Marzocchi, 169 U.S.P.Q. 367, C.C.P.A., 1971). The level of skill in the relevant art is high, and one of ordinary skill in the art could readily practice the invention without the expense of undue experimentation.

In view of the foregoing, Applicants respectfully maintain that the invention as claimed is adequately enabled, and the withdrawal of the rejection is requested.

The Rejections under 35 U.S.C. 102

Claims 16, 18 and 20 remain rejected under 35 U.S.C. 102(b) as allegedly anticipated by Takao et al. (1996) and Yajima et al. (1995). Applicants respectfully traverse this rejection.

The Takao reference

The Patent Office has alleged that SEQ ID NO:2, amino acids 230-828, is taught at Fig. 2 (pg. 1269) and the incision assay for double-stranded DNA is described at page 1268.

A careful reading of the Takao reference reveals that this reference teaches that the truncated endonuclease was not stable in pure form, and that the assays were carried out with endonuclease preparations which were only about 35% pure. See page 1269, column 1. By contrast, the present application teaches that the truncated UVDE proteins were purified to apparent electrophoretic homogeneity and that the proteins made were stable in pure form. New claims 21 specifies that the endonuclease based on SEQ ID NO:2, amino acids 230-828, is purified. Claim 25 does not recite UveP1 enzyme use (as set forth in SEQ ID NO:2 or NO:4. Thus, Applicants respectfully submit that the present claimed invention is distinguished over the teachings of the cited Takao reference. The purified endonuclease preparations of the prior art were not stable, as are those taught in the present application. Thus, the present method claim

specifies that the endonuclease is purified. In view of the different properties of Applicants' enzyme preparation, it is clearly not the same as that of the cited prior art.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have canceled claims 16, 18 and 20 without prejudice and have presented new claims which do not recite the use of DNA damaged by UV irradiation or containing photoproducts. New claims 21 and 23 recite the use of the endonuclease consisting of the amino acid sequence of SEQ ID NO:2 (GST-truncated UVeP1) for action on UV-irradiated DNA and DNA containing photoproducts causing distortion. SEQ ID NO:2 is not taught by the cited reference.

Accordingly, the present invention as now claimed is not anticipated by the cited Takao reference, and the rejection must be withdrawn.

The Yajima reference

The Patent Office has alleged that SEQ ID NO:36 is shown in Fig. 2 (pg. 2394) and the incision assay is taught at page 2399.

The cited Yajima reference relates to UV damage specific endonuclease from *Neurospora crassa.* The first incision assay taught at page 2399 is one in which closed circular plasmid DNA has been UV-irradiated. The second assay is one in which oligonucleotides with pyrimidine dimers have been UV-irradiated.

Without acquiescing to this rejection and in the interest of advancing prosecution, Applicants have canceled claims 16 and 18 without prejudice, and new claim 25 does not recite photoproducts or UV-irradiated DNA.

In view of the amendments to the claims, Applicants respectfully urge that the cited Yajima reference does not anticipate the invention as presently claimed, and the withdrawal of the rejection is requested.

Claims 16-20 have been newly rejected under 35 U.S.C. 102(b) as allegedly anticipated by Takao et al. (1996). Applicants respectfully traverse this rejection.

The Patent Office has alleged that the Takao reference teaches the cloning of the UVDE gene and that a protein truncated up to 230 amino acids retains enzymatic activity. SEQ ID NO:4 is allegedly identical to the truncated enzyme of Figure 5B of the reference. The Patent Office has concluded that the claimed method of use is anticipated by the cited Takao et al. reference.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have canceled claims 16-20. The newly presented claims do not recite cleavage of a UV-irradiated substrate or a substrate containing a photoproduct when the endonuclease is the truncated enzyme.

In view of the foregoing, Applicants respectfully submit that the invention as presently claimed is not anticipated by the cited reference, and the withdrawal of the rejection is requested.

The Rejection under 35 U.S.C. 103

Claims 16, 18 and 20 have been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Bellacosa et al. (1999) and further in view of common knowledge in the filed of DNA repair and practice in DNA repair studies. Applicants respectfully traverse this rejection.

The claims are directed to the method for cleavage of double stranded DNA containing a distorted structure when the cleavage enzyme has the amino acid sequence of SEQ ID NO:38. The Bellacosa reference teaches SEQ ID NO:38 is presented in Fig. 2 (pg. 3972). The reference is said to teach an incision assay of the DNA at page 3970. No results of the use of the enzyme and assay are said to be taught in the case of UV damaged DNA. However, the authors are said to suggest clarifying the role of the new enzyme in mismatch repair and predict the possibility that MED1 functions in a pathway of base excision repair (page 3974, right column, line13). The Examiner has alleged that it would have been obvious to use the enzyme

in an assay for cleavage of DNA irradiated with UV or other DNA damaging agent because the DNA repair process involve mismatching of nucleotides in pairing. The Examiner has alleged that Bellacosa provides motivation to use the enzyme in characterization of the mismatch repair process in human as well as a possible medicinal use. The Examiner has further alleged that the expectation of success is high because of the teachings of the enzyme's properties.

Applicants respectfully maintain that the method for DNA cleavage taught at page 3970 of the cited Bellacosa reference is a method for cleavage of supercoiled plasmid DNA. There is no indication in this cited reference that the DNA contains any distortion(s) corresponding to those particularly recited in the instant claims. In the absence of any specific notation of mismatch, photoproducts, loop, etc., one of ordinary skill in the art will assume that there is no distortion in the supercoiled DNA.

Applicants respectfully submit that Bellacosa's statement at page 3974, left column, line 13, is properly characterized as an invitation to experiment, and that an invitation to experiment is not a proper basis for a rejection under 35 U.S.C. 103. The reference states "the possibility that MED1 functions in a pathway of base excision repair should be taken into consideration. The Bellacosa reference provides data that the MED protein has endonuclease activity using supercoiled plasmid DNA and that it interacts with the MLH1.

In view of the foregoing clarification of the teaching of the endonuclease assay in the cited Bellacosa reference, Applicants respectfully maintain that the cited reference does not render obvious the invention as claimed, and that the rejection must be withdrawn.

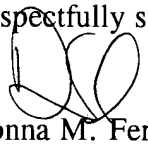
Conclusion

In view of the foregoing, it is submitted that this case is in condition for allowance, and passage to issuance is respectfully requested.

If there are any outstanding issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This Amendment is accompanied by a Petition for Extension of Time (three months) and authorization to charge the fee of $465.00 as required by 37 C.F.R 1.17 to Deposit Account No. 07-1969. It is believed that this amendment does not necessitate the payment of any additional fees under 37 C.F.R. 1.16-1.17. If the amount submitted is incorrect, however, please charge any deficiency or credit any overpayment to Deposit Account No. 07-1969.

Respectfully submitted,



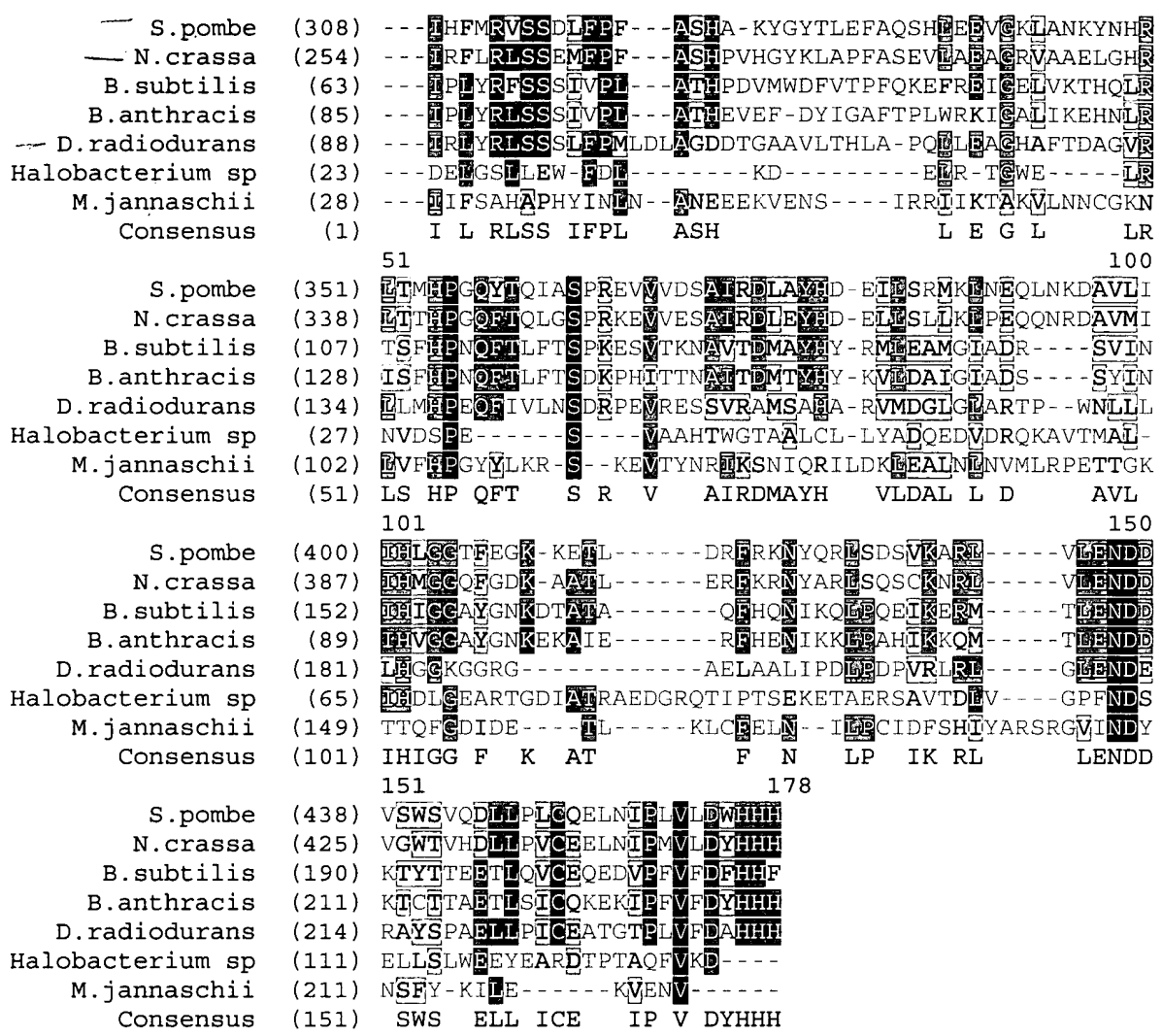
Donna M. Ferber
Reg. No. 33,878

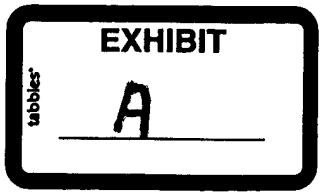
GREENLEE, WINNER AND SULLIVAN, P.C.
5370 Manhattan Circle, Suite 201
Boulder, CO 80303
Phone (303) 499-8080
Fax (303) 499-8089
bmk: March 20, 2003
Docket 25-98A

Marked up version of amended paragraph in attached Amendment.

In the Specification, pages 43-44, bridging paragraph, please amend as follows:

Homologs of the *S. pombe* UVDE protein have been identified by BLAST searching of sequence database (Genbank, TIGR) using the UVDE amino acid sequence: *N. crassa* (Genbank Accession No. BAA 74539), *B. subtilis* (Genbank Accession No. 249782), human (Genbank Accession No. AF 114784.1, methyl-CpG binding endonuclease) and a *Deinococcus radiodurans* sequence located from the TIGR database. The amino acid sequences of these proteins are given in SEQ ID NO:36 (*N. crassa*), SEQ ID NO:37 (*B. subtilis*), SEQ ID NO:38 (*Homo sapiens*) and SEQ ID NO:39 *(D. radiodurans*). The *D. radiodurans* coding sequence can be generated using the genetic code and codon choice according to the recombinant host in which the protein is to be expressed, or the natural coding sequence can be found on the TIGR database, *D. radiodurans* genomic sequence in the region between bp 54823 and 60981. Additional homologs of the *S. pombe* UVDE include the UV damage enzyme of *Bacillus anthracis*; *Halobacterium* sp., disclosed in Genbank Accession No. AAC 82899; *Methanococcus jannaschii,* disclosed in Genbank Accession No. 057597; and *Thermotoga maritima*, disclosed in Genbank Accession No. AE001740. These homologs were identified using Blast or FastA on the NCBI or TIGR websites. A Uve1p consensus sequence has been derived using the vector NTI AlignX program. This consensus sequence spans amino acids 308-465 of the C-terminal region of the *S. pombe* Uve1p. This region shows significant sequence similarity to portions of the *B. subtilis* and *N. crassa* Uve1p equivalents. ~~The alignments for this region are shown in Table 19. The partial amino acid sequences of the *Bacillus anthracis*, *Halobacterium* sp., *Methanococcus jannaschii*, and *Thermotoga maritima* are provided in SEQ ID Nos: 72-75. The consensus sequence is given in SEQ ID NO:76, and the sequence alignment and consensus sequence are illustrated in Table 24.~~


S.pombe (308) ---IHFMRVSSDLFPF---ASHA-KYGYTLEFAQSHEEEVGKLANKYNHK
N.crassa (254) ---IRFLRLSSEMFPF---ASHPVHGYKLAPFASEVLAEAGRVAAELGHK
B.subtilis (63) ---IPLYRFSSSIVPL---ATHPDVMWDFVTPFQKEFREICELVKTHQLR
B.anthracis (85) ---IPLYRLSSSIVPL---ATHEVEF-DYIGAFTPLWRKICALIKEHNLR
D.radiodurans (88) ---IRLYRLSSSLFPMLDLAGDDTGAAVLTHLA-PQLLEAGHAFTDAGVR
Halobacterium sp (23) ---DELGSLLEW-FDL--------KD---------ELR-TGWE-----LR
M.jannaschii (28) ---IIFSAHAPHYINLN--ANEEEKVENS----IRRIIKTAKVLNNCGKN
Consensus (1) I L RLSS IFPL ASH L E G L LR
51 100
S.pombe (351) LTMHPGQYTQIASPREVVVDSAIRDLAYHD-EILSRMKLNEQLNKDAVLI
N.crassa (338) LIIHPGQFTQLGSPRKEVVESAIRDLEYHD-ELLSLLKLPEQQNRDAVMI
B.subtilis (107) TSFHPNQFTLFTSPKESVTKNAVTDMAYHY-RMLEAMGIADR----SVIN
B.anthracis (128) ISFHPNQFTLFTSDKPHITTNAITDMTYHY-KVLDAIGIADS----SYIN
D.radiodurans (134) LLMHPEQFIVLNSDRPEVRESSVRAMSAHA-RVMDGLGLARTP--WNLLL
Halobacterium sp (27) NVDSPE------S----VAAHTWGTAALCL-LYADQEDVDRQKAVTMAL-
M.jannaschii (102) LVFHPGYYLKR-S--KEVTYNRIKSNIQRILDKLEALNLNVMLRPETTGK
Consensus (51) LS HP QFT S R V AIRDMAYH VLDAL L D AVL
101 150
S.pombe (400) IHLGGTFEGK-KETL------DRFRKNYQRLSDSVKARL-----VLENDD
N.crassa (387) IHMGGQFGDK-AATL------ERFKRNYARLSQSCKNRL-----VLENDD
B.subtilis (152) IHIGGAYGNKDTATA-------QFHQNIKQLPQEIKERM-----TLENDD
B.anthracis (89) IHVGGAYGNKEKAIE-------RFHENIKKLPAHIKKQM-----TLENDD
D.radiodurans (181) LHGGKGGRG-----------AELAALIPDLPDPVRLRL-----GLENDE
Halobacterium sp (65) IHDLGEARTGDIATRAEDGRQTIPTSEKETAERSAVTDLV----GPFNDS
M.jannaschii (149) TTQFGDIDE----IL-----KLCPELN--ILPCIDFSHIYARSRGVINDY
Consensus (101) IHIGG F K AT F N LP IK RL LENDD
151 178
S.pombe (438) VSWSVQDLLPLCQELNIPLVLDWHHH
N.crassa (425) VGWTVHDLLPVCEELNIPMVLDYHHH
B.subtilis (190) KTYTTEETLQVCEQEDVPFVFDFHHF
B.anthracis (211) KTCITAETLSICQKEKIPFVFDYHHH
D.radiodurans (214) RAYSPAELLPICEATGTPLVFDAHHH
Halobacterium sp (111) ELLSLWEEYEARDTPTAQFVKD----
M.jannaschii (211) NSFY-KILE------KVENV------
Consensus (151) SWS ELL ICE IP V DYHHH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